University: The University of Hong Kong (HKU)

Faculty: Li Ka Shing Faculty of Medicine

Title of case study: Knowledge Exchange on HIV/AIDS to promote HIV prevention and care

(1) Summary of the impact (indicative maximum 100 words)

Our team has done tremendous amount of KE work in promoting HIV prevention and care in Hong Kong and in China during the past decade, and has achieved significant impacts in the following areas: A) Governmental policies and guidelines, B) Public awareness, C) Community education, and D) Biomedical industry development. Here, we present our discovery of PD1-based vaccine for HIV-1 immunotherapy, which has led to multiple high impact publications, a HKU patent, improved HIV awareness, better community education, a biomedical startup company Immuno Cure in Hong Kong, and the subsequent success of our 2018/2019 TRS grant for the vaccine clinical development.

(2) Underpinning research (indicative maximum 500 words)

With previous supports from RGC General Research Fund/Collaborative Research Fund and Health and Medical Research Fund (HMRF), we have made some important findings, leading to HKU-patented technology on programmed death-1 (PD1)-based vaccine. HIV-1-specific $CD8^+$ T lymphocytes are essential for suppressing viral replication, yet few vaccine candidates could elicit such cellular immunity. We hypothesize that PD1-based vaccine immunotherapy will provide a prolonged viremia control by potentiating host immunity. This hypothesis is mainly based on the following discoveries.

In our first study, we reported the development of a novel antigen-targeting DNA vaccine strategy that exploits the binding of PD1 to its ligands expressed on dendritic cells (DCs) by fusing soluble PD1 with HIV-1 GAG p24 antigen (*Journal of Clinical Investigation* 2013*, Molecular Therapy-Cell Press* 2013). As compared with non-DC-targeting vaccines, intramuscular immunization via electroporation (EP) of the PD1-based vaccine in mice elicited consistently high frequencies of GAG-specific, broadly reactive, polyfunctional, long-lived, and cytotoxic $CD8^+$ T cells and robust anti-GAG antibody titers. Vaccination conferred remarkable protection against mucosal challenge with a vaccinia-GAG virus. We found that PD1-based vaccination potentiated $CD8^+$ T cell responses by enhancing antigen binding and uptake in DCs and activation in the draining lymph node. It also increased IL-12-producing DCs and engaged antigen cross-presentation when compared with the anti-DEC205 antibody-mediated DC targeting approach. The high frequency of durable and protective GAG-specific $CD8^+$ T cell immunity induced by PD1-based vaccination suggests that this vaccine strategy could potentially be used against HIV-1 and other pathogens. In the meantime, PD1-based vaccines also displayed potential for cancer immunotherapy (*Cancer Research* 2014).

Considering that HIV-1 functional cure requires sustained viremia control without antiretroviral therapy, we further investigated PD1-based vaccine in non-human primate models. We designed a recombinant DNA vaccine that targets the simian immunodeficiency virus (SIV) capsid antigen to DC via a fused rhesus soluble PD1 domain. Homologous PD1-based DNA vaccination suppressed setpoint viremia to undetectable levels in all rhesus macaques tested following high-dose intravenous challenge with pathogenic simian-human immunodeficiency virus $SHIV_{SF162P3}$. The vaccine induced high frequencies of polyfunctional effector-memory $CD8^+$ T cells, which were re-called potently upon the viral challenge. All vaccinated macaques under long-term observation showed sustained viremia control for over 2 years. Depleting $CD8^+$ T cells resulted in transient viremia, highlighting the involvement of vaccine-induced $CD8^+$ T cells in $SHIV_{SF162P3}$ control. In summary, the PD1-based vaccination shows potential as a straightforward approach

towards a functional SIV/HIV cure.

Based on these critical findings, this vaccination method has been patented by HKU TTO for technology transfer, which resulted in the establishment of a biomedical company called **Immuno Cure Ltd Hong Kong** through the TSSSU@HKU award. With promising progresses made, we have successfully obtained the UICP grant (UIM/314, HK$21m) in 2017 for GMP-manufacturing the PD1-based vaccine and later the 2018/2019 RGC TRS grant (T11-706/18-N, HK$47m) for mechanism and translational studies on combined PD1-based vaccine and tandem bispecific neutralizing antibody (*Journal of Clinical Investigation* 2018) in monkey models and human subjects. Therefore, our discovery has been moved from laboratory towards clinical trials, which is remarkable.

(3) References to the research (indicative maximum of six references)

Zhou J, Cheung AKL, Tan Z, Wang H, Du Y, Kang Y, Lu X, Liu L, Yuen KY and **Chen Z***. PD1-based DNA vaccine amplifies HIV-1 GAG-specific $CD8^+$ T cells in mice. ***Journal of Clinical Investigation*.** 2013 Jun;123(6):2629-42. doi: 10.1172/JCI64704. Epub 2013 May 1.

Zhou J, Cheung AKL, Liu H, Tan Z, Tang X, Kang Y, Du Y, Wang H, Liu L, and **Chen Z***. Potentiating functional antigen-specific CD8+ T cell immunity by a novel PD1 isoform-based fusion DNA vaccine. ***Molecular Therapy* (*Cell Press*).** 2013 Jul;21(7):1445-55.

Tan Z, Zhou J, Cheung AK, Yu Z, Cheung KW, Liang J, Wang H, Lee BK, Man K, Liu L, Yuen KY, **Chen Z***. Vaccine-elicited CD8+ T cells cure mesothelioma by overcoming tumor-induced immunosuppressive environment. ***Cancer Research***. 2014 Nov 1;74(21):6010-21.

Cheng L, Tang X, Liu L, Peng J, Nishiura K, Cheung AK, Guo J, Wu X, Tang HY, An M, Zhou J, Cheung KW, Wang H, Guan X, Wu Z, **Chen Z***. Monoclonal antibodies specific to human Δ42PD1: A novel immunoregulator potentially involved in HIV-1 and tumor pathogenesis. ***MAbs***. 2015 May 4;7(3):620-9.

Cheung AKL, Kwok HY, Huang Y, Chen M, Mo Y, Wu X, Lam KS, Kong HK, Lau TCK, Zhou J, Li J, Cheng L, Kiat Lee B, Peng Q, Lu X, An M, Wang H, Shang H, Zhou B, Wu H, Xu A, Yuen KY, **Chen Z***. Gut-homing Δ42PD1+Vδ2 T cells promote innate mucosal damage via TLR4 during acute HIV type 1 infection. ***Nature Microbiology***. 2017 Oct;2(10):1389-1402.

Wu X, Guo J, Niu M, An M, Liu L, Wang H, Jin X, Zhang Q, Lam KS, Wu T, Wang H, Wang Q, Du Y, Li J, Cheng L, Tang HY, Shang H, Zhang L, Zhou P, **Chen Z***. Tandem bispecific neutralizing antibody eliminates HIV-1 infection in humanized mice. ***Journal of Clinical Investigation***. 2018 Jun 1;128(6):2239-2251. doi: 10.1172/JCI96764. Epub 2018 Apr 23. pii: 96764. doi: 10.1172/JCI96764.

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(4) Details of the impact (indicative maximum 750 words)

HIV-1 is the causative agent of AIDS. To date, HIV-1 continues to spread, leading to 36.9 million people living with the virus and about 40 million deaths worldwide. In Hong Kong, despite aggressive prevention programs and timely introduction of antiretroviral therapy (ART), the number of cumulative infections has increased from 776 in 1996 to 9715 in 2018. Financially, ART expense alone has increased to estimated HK$550 millions in 2017-18. Since the life-long ART is unlikely sustainable and does not cure HIV/AIDS, our research objective is to discover an effective immunotherapy of potentiating host immunity to achieve a functional cure, a state of suppressed viremia below detection limit for a prolonged period in HIV-infected patients without

receiving ART. This would significantly reduce the adverse effects of the ART in patients and the financial burdens to the governments and patients.

For this purpose, we proposed to prove the concept of PD1-based vaccine and successfully won a RGC GRF grant. After we found that PD1-based vaccine preferentially induces antigen-specific $CD8^+$ T cells, this discovery quickly generated KE impacts in several areas. First, we filed the initial patent application in 2010, followed by receiving the complete patent (US 9,029,315 B2) in 2015 via HKU TTO. Second, our results were officially published in *Journal of Clinical Investigation* in 2013, which led to the Award for Outstanding Research Postgraduate Student by HKU Graduate School to give due recognition to the research postgraduate student who has submitted a thesis of exceptional quality and has demonstrated outstanding performance in other academic aspects. Third, HKU press release on our findings caught extensive press coverage, which promoted the awareness of HIV/AIDS prevention and care in Hong Kong and in Mainland China. Fourth, the Hong Kong AIDS Foundation then invited Prof. Chen to give a lecture on PD1-based vaccine and its implication to HIV prevention in a local symposium. Several hundreds of people attended the event with the theme entitled "We stay together forever", which enhances KE in local communities. Fifth, due to the discovery of PD1-based vaccine, Prof. Chen was invited to give lectures in several world-renown institutions including US National Institutes of Health, The Institut Pasteur in Paris, The Ragon Institute of Massachusetts General Hospital (MGH)/Massachusetts Institute of Technology (MIT)/Harvard University, Aaron Diamond AIDS Research Center of the Rockefeller University, and The Peter Doherty Institute for Infection and Immunity. Sixth, as an invited speaker, Prof. Chen gave an oral presentation on PD1 vaccine-based immunotherapy in Madrid at HIVR4P, the world's first and only international scientific meeting dedicated exclusively to biomedical HIV prevention research. Seventh, with the help by HKU TTO, we successfully won the TSSSU@HKU award in 2015 and started a local biomedical company, namely Immuno Cure Ltd Hong Kong, allowing human PD1-based vaccine for research and development. Eighth, based on our satisfactory performance of the TSSSU@HKU, we have further been awarded a UICP grant in 2017, entitled "A Novel PD1-based Vaccine for HIV/AIDS Immunotherapy". Lastly, by securing the GMP production of PD1-based Vaccine for HIV/AIDS Immunotherapy through the UICP grant (UIM/314), we were able to construct a team of researchers winning the only HKU RGC TRS award in 2018/2019 (TRS:T11-706/18-N), entitled "Potentiating Host Immunity for HIV-1 Functional Cure". Notably, we also contributed significantly to the governmental "Recommended HIV/AIDS Strategies for Hong Kong 2017-2012", "HIV manual", "International AIDS Society global scientific strategy: towards an HIV cure 2016" (Nat. Med. 2016), and the 2019 "China New Development Award"-wining book "HIV Vaccines and Cure" (Springer Nature).

In summary, we were the first group in the world reporting PD1-based vaccine that promotes the induction of HIV-specific $CD8^+$ T cells capable of eliminating virus-infected cells in animal models. Based on this discovery, our KE activities involved a broad range of impacts as mentioned above, which not only achieved the technological transfer of our patent to develop a biomedical company and public awareness of HIV prevention and care in Hong Kong, but also signified the strategical importance of HKU in the fight against the global HIV/AIDS pandemic.

(5) Sources to corroborate the impact (indicative maximum of 10 references)

1. Award for Outstanding Research Postgraduate Student (HKU) publication:
   Zhou J, Cheung AKL, Tan Z, Wang H, Kang Y, Du Y, Lu X, Liu L, Yuen KY and Chen Z*. PD1-based DNA vaccine amplifies HIV-1 GAG-specific CD8+ T cells in mice. *Journal of Clinical Investigation*. 2013 Jun 3;123(6):2629-42.
2. HKU patent: No.: US 9,029,315 B2, Date: May 12, 2015; Patent: Soluble PD-1 Variants, Fusion Constructs, and Uses Thereof.
3. Hong Kong news coverage on our discovery after the HKU press release:

October 25, 2013

人民日報: "香港大學陳志偉博士完成愛滋病黏膜疫苗前期臨床研究，取得國際專利 - 二十年如一日抗愛滋"

September, 2013

Networking Voice by Red Ribbon Center: 愛滋病疫苗的研究進展'

May 20, 2013

Wen Wei Po: '公共衛生：港產愛滋剋星'

May 16, 2013

Metropolis Daily: '港大成功研愛滋苗'

Hong Kong Economic Times: '港大研基因疫苗 冀可治愛滋'

Sky Post: '愛滋基因疫苗 清除8成病毒'

Yahoo Hong Kong: '港大研抗愛滋DNA疫苗'

Discuss.com.hk:

'港大醫學院發明全球第一支愛滋病疫苗'

Sina Hong Kong: '港大研抗愛滋DNA疫苗'

May 16, 2013

南华早报: 港大发明艾滋病新疫苗

SCMP: 'HKU scientists find potential new HIV drug'

SCMP: 'Insight & Opinion - HIV treatment - Who said it?'

Apple Daily News: '港大研發DNA疫苗 刺激細胞滅愛滋'

The Standard: "Hopeful' step taken to HIV vaccine'

Oriental Daily News: '新疫苗殺死愛滋病毒'

May 15, 2013

'HKU discovers a novel DNA vaccine which can induce a high frequency of CD8+T cells to combat Aids - A new strategy for designing AIDS vaccine'

'HKU discovers a novel DNA vaccine which can induce a high frequency of CD8+T cells to combat Aids - A new strategy for designing AIDS vaccine'

World News: "Hopeful' step taken to HIV vaccine'

4. Invited lecture by Hong Kong AIDS Foundation for hundreds of local community people on our PD1-based vaccine in 2013.

5. Invited lectures at world-leading research institutions and universities to exchange our findings on PD1-based vaccine including (1) US National Institute of Health for The Neuroscience Consortium Cutting Edge Symposium, (2) The Ragon Institute of MGH, MIT and Harvard, (3) The Aaron Diamond AIDS Research Center of Rockefeller University, and (4) Institut Pasteur in Paris.
6. Invited speakers at international meetings including HIVR4P, the world's first and only international scientific meeting dedicated exclusively to biomedical HIV prevention research in Madrid, and The International Global Virus Network (GVN) Meeting hosted by The Peter Doherty Institute for Infection and Immunity in Australia.
7. TSSSU@HKU award, TSSSU/HKU/15/02/1; Date: May 2015 – April 2016, "PD1-BASED DNA VACCINE FOR AIDS"
8. UICP grant award, UICP: UIM/314 "A Novel PD1-based Vaccine for HIV/AIDS Immunotherapy"
9. RGC TRS award, TRS: T11-706/18-N "Potentiating Host Immunity for HIV-1 Functional Cure" in 2018/2019.
10. Invited Speakers in 2019, (1) Cent Gardes Conference: HIV Vaccine, "This biennial symposium gathers international speakers of the highest level together"; (2) The 6th National Academic Conference on HIV/AIDS, "是我国艾滋病防治领域水平最高、最为盛大的学术交流活动"